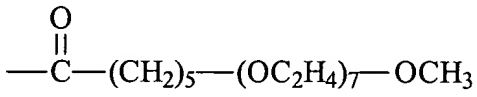
IN THE CLAIMS

Please amend the claims as follows.

1. (Currently amended) A mixture of conjugates, each comprising ~~a human~~ an insulin drug coupled to an oligomer having a formula:



wherein the mixture has a dispersity coefficient (DC) greater than 10,000, where

$$DC = \frac{\left(\sum_{i=1}^{n} N_i M_i\right)^2}{\sum_{i=1}^{n} N_i M_i^2 \sum_{i=1}^{n} N_i - \left(\sum_{i=1}^{n} N_i M_i\right)^2}$$

wherein:

n is the number of different molecules in the sample;

N_i is the number of i^{th} molecules in the sample; and

M_i is the mass of the i^{th} molecule.

2. (Original) The mixture according to Claim 1, wherein the dispersity coefficient is greater than 100,000.

3. (Original) The mixture according to Claim 1, wherein the dispersity coefficient is greater than 500,000.

4-6. (Canceled)

7. (Currently amended) The mixture according to Claim 1, wherein the insulin drug is human insulin and the oligomer is covalently coupled to Lys^{B29} of the human insulin ~~drug~~.

8. (Original) The mixture according to Claim 1, wherein the mixture has an *in vivo* activity that is greater than the *in vivo* activity of a polydispersed mixture of insulin drug-oligomer conjugates having the same number average molecular weight as the mixture.

9. (Original) The mixture according to Claim 1, wherein the mixture has an *in vitro* activity that is greater than the *in vitro* activity of a polydispersed mixture of insulin drug-oligomer conjugates having the same number average molecular weight as the mixture.

10. (Currently amended) The mixture according to Claim 1, wherein the ~~human~~ insulin-drug oligomer has an increased resistance to degradation by chymotrypsin when compared to the resistance to degradation by chymotrypsin of a polydispersed mixture of insulin drug-oligomer conjugates having the same number average molecular weight as the mixture.

11. (Original) The mixture according to Claim 1, wherein the mixture has an inter-subject variability that is less than the inter-subject variability of a polydispersed mixture of insulin drug-oligomer conjugates having the same number average molecular weight as the mixture.

12-15. (Canceled)

16. (Currently amended) A mixture of conjugates, each comprising human insulin coupled to an oligomer that comprises a polyethylene glycol moiety, wherein the mixture has a dispersity coefficient (DC) greater than 10,000, where

$$DC = \frac{\left(\sum_{i=1}^{n} N_i M_i\right)^2}{\sum_{i=1}^{n} N_i M_i^2 \sum_{i=1}^{n} N_i - \left(\sum_{i=1}^{n} N_i M_i\right)^2}$$

wherein:

n is the number of different molecules in the sample;

N_i is the number of i^{th} molecules in the sample; and

M_i is the mass of the i^{th} molecule; and

wherein the conjugate comprises a first oligomer and a second oligomer; and

wherein the first oligomer is covalently coupled at Lys^{B29} of the insulin and the second oligomer is covalently coupled at N-terminal A1 or N-terminal B1 of the insulin.

17. (Currently amended) The mixture according to Claim 1, wherein the ~~human~~ insulin drug is covalently coupled to the oligomer.

18. (Previously presented) The mixture according to Claim 16, wherein the insulin is covalently coupled to at least one of the oligomers by a hydrolyzable bond.

19. (Previously presented) The mixture according to Claim 16, wherein the insulin is covalently coupled to the polyethylene glycol moiety of at least one of the oligomers.

20. (Previously presented) The mixture according to Claim 16, wherein at least one of the oligomers comprises a lipophilic moiety covalently coupled to the polyethylene glycol moiety.

21. (Previously presented) The mixture according to Claim 16, wherein at least one of the oligomers comprises a lipophilic moiety.

22. (Previously presented) The mixture according to Claim 21, wherein the insulin is covalently coupled to the lipophilic moiety.

23. (Original) The mixture according to Claim 21, wherein the polyethylene glycol moiety is covalently coupled to the lipophilic moiety.

24. (Original) The mixture according to Claim 1, wherein the conjugate comprises a first oligomer and a second oligomer.

25. (Previously presented) The mixture according to Claim 16, wherein the first and the second oligomers are the same.

26. (Previously presented) The mixture according to Claim 16, wherein at least one of the oligomers comprises a first polyethylene glycol moiety covalently coupled to the insulin by a non-hydrolyzable bond and a second polyethylene glycol moiety covalently coupled to the first polyethylene glycol moiety by a hydrolyzable bond.

27. (Previously presented) The mixture according to Claim 26, wherein the oligomer(s) comprising a first polyethylene glycol moiety covalently coupled to the insulin by a non-hydrolyzable bond and a second polyethylene glycol moiety covalently coupled to the first polyethylene glycol moiety by a hydrolyzable bond further comprise a lipophilic moiety covalently coupled to the second polyethylene glycol moiety.

28. (Previously presented) The mixture according to Claim 16, wherein each of the conjugates is amphiphilically balanced such that each conjugate is aqueously soluble and able to penetrate biological membranes.

29. (Original) A pharmaceutical composition comprising:

the mixture according to Claim 1; and

a pharmaceutically acceptable carrier.

30. (Currently amended) A method of treating insulin deficiency in a subject in need of such treatment, said method comprising:

administering an effective amount of the ~~composition~~ mixture of claim 1 to the subject to treat the insulin deficiency.

31-39. (Canceled)

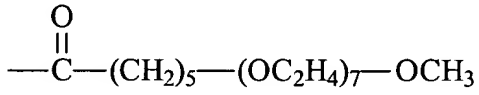
40. (Original) A substantially monodispersed mixture of conjugates each comprising human insulin covalently coupled at Lys^{B29} of the human insulin to the carboxylic acid moiety of a carboxylic acid, which is covalently coupled at the end distal to the carboxylic acid moiety to a methyl terminated polyethylene glycol moiety having at least 7 polyethylene glycol subunits.

41. (Currently amended) The substantially monodispersed mixture according to Claim 40, wherein ~~the conjugates each consist of human insulin covalently coupled at Lys^{B29} of the human insulin to~~ the carboxylic acid ~~moiety of~~ is hexanoic acid~~, which is covalently coupled at the end distal to the carboxylic acid moiety to a methyl terminated polyethylene glycol moiety having 7 polyethylene glycol subunits~~.

42-45. (Canceled)

46. (Currently amended) A mixture of conjugates, each comprising ~~an~~ human insulin ~~drug~~ coupled to an oligomer that comprises a polyethylene glycol moiety, said mixture having a

molecular weight distribution with a standard deviation of less than about 22 Daltons, wherein ~~the insulin drug is human insulin, and~~ the oligomer is covalently coupled to Lys^{B29} of the human insulin and has the formula:



47. (Original) The mixture according to Claim 46, wherein the standard deviation of the molecular weight distribution is less than about 14 Daltons.

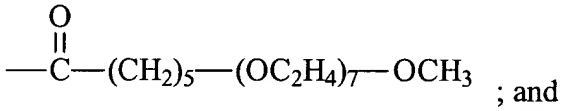
48. (Original) The mixture according to Claim 46, wherein the standard deviation of the molecular weight distribution is less than about 11 Daltons.

49. (Canceled)

50. (Currently amended) A mixture of conjugates, each comprising ~~an~~ human insulin ~~drug~~ coupled to an oligomer that comprises a polyethylene glycol moiety,

wherein each polyethylene glycol moiety has the same number of polyethylene glycol subunits,

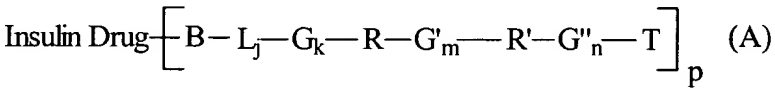
wherein each oligomer is covalently coupled to Lys^{B29} of the human insulin and has the formula:


; and

wherein the mixture has a molecular weight distribution with a standard deviation of less than about 22 Daltons.

51. (Canceled)

52. (Previously presented) A mixture of conjugates in which each conjugate is the same and has the formula:



(A)

wherein:

B is carbonyl;

L is a linker moiety;

G, G' and G" are individually selected spacer moieties;

R is C_5 alkylene and R' is polyethylene glycol having 7 polyethylene glycol subunits;

T is methoxy;

j is 0 or 1;

k, m and n are 0; and

p is an integer from 1 to the number of nucleophilic residues on the insulin drug.

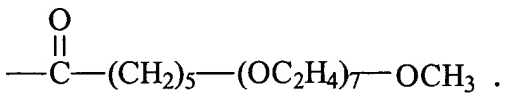
53-67. (Canceled)

68. (Previously presented) The mixture according to claim 16, wherein at least one of the oligomers comprises a polyethylene glycol moiety having at least 2 polyethylene glycol subunits.

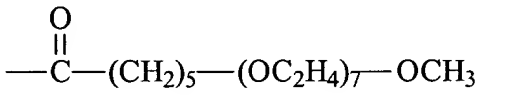
69. (Previously presented) The mixture according to claim 16, wherein at least one of the oligomers comprises a polyethylene glycol moiety having at least 5 polyethylene glycol subunits.

70. (Previously presented) The mixture according to claim 16, wherein at least one of the oligomers comprises a polyethylene glycol moiety having at least 7 polyethylene glycol subunits.

71. (Currently amended) The mixture according to claim 16, wherein ~~at least one of the oligomers is covalently coupled to Lys^{B29} of the human insulin and~~ the first oligomer has the formula:



72. (New) A substantially monodispersed mixture of conjugates, each comprising an insulin drug coupled to an oligomer having a formula:



73. (New) The mixture according to Claim 72, wherein the mixture is monodispersed.

74. (New) The mixture according to Claim 72, wherein the insulin drug is human insulin and the oligomer is covalently coupled to Lys^{B29} of the human insulin.

75. (New) The mixture according to Claim 72, wherein the mixture has an *in vivo* activity that is greater than the *in vivo* activity of a polydispersed mixture of insulin drug-oligomer conjugates having the same number average molecular weight as the mixture.

76. (New) The mixture according to Claim 72, wherein the mixture has an *in vitro* activity that is greater than the *in vitro* activity of a polydispersed mixture of insulin drug-oligomer conjugates having the same number average molecular weight as the mixture.

77. (New) The mixture according to Claim 72, wherein the insulin-drug oligomer has an increased resistance to degradation by chymotrypsin when compared to the resistance to degradation by chymotrypsin of a polydispersed mixture of insulin drug-oligomer conjugates having the same number average molecular weight as the mixture.

78. (New) The mixture according to Claim 72, wherein the mixture has an inter-subject variability that is less than the inter-subject variability of a polydispersed mixture of insulin drug-oligomer conjugates having the same number average molecular weight as the mixture.

79. (New) A substantially monodispersed mixture of conjugates, each comprising human insulin coupled to an oligomer that comprises a polyethylene glycol moiety,

wherein the conjugate comprises a first oligomer and a second oligomer; and

wherein the first oligomer is covalently coupled at Lys^{B29} of the insulin and the second oligomer is covalently coupled at N-terminal A1 or N-terminal B1 of the insulin.

80. (New) The mixture according to Claim 72, wherein the insulin drug is covalently coupled to the oligomer.

81. (New) The mixture according to Claim 79, wherein the insulin is covalently coupled to at least one of the oligomers by a hydrolyzable bond.

82. (New) The mixture according to Claim 79, wherein the insulin is covalently coupled to the polyethylene glycol moiety of at least one of the oligomers.

83. (New) The mixture according to Claim 79, wherein at least one of the oligomers comprises a lipophilic moiety covalently coupled to the polyethylene glycol moiety.

84. (New) The mixture according to Claim 79, wherein at least one of the oligomers comprises a lipophilic moiety.

85. (New) The mixture according to Claim 84, wherein the insulin is covalently coupled to the lipophilic moiety.

86. (New) The mixture according to Claim 84, wherein the polyethylene glycol moiety is covalently coupled to the lipophilic moiety.

87. (New) The mixture according to Claim 72, wherein the conjugate comprises a first oligomer and a second oligomer.

88. (New) The mixture according to Claim 79, wherein the first and the second oligomers are the same.

89. (New) The mixture according to Claim 79, wherein the mixture is monodispersed.

90. (New) The mixture according to Claim 79, wherein at least one of the oligomers comprises a first polyethylene glycol moiety covalently coupled to the insulin by a non-

hydrolyzable bond and a second polyethylene glycol moiety covalently coupled to the first polyethylene glycol moiety by a hydrolyzable bond.

91. (New) The mixture according to Claim 90, wherein the oligomer(s) comprising a first polyethylene glycol moiety covalently coupled to the insulin by a non-hydrolyzable bond and a second polyethylene glycol moiety covalently coupled to the first polyethylene glycol moiety by a hydrolyzable bond further comprise a lipophilic moiety covalently coupled to the second polyethylene glycol moiety.

92. (New) The mixture according to Claim 79, wherein each of the conjugates is amphiphilically balanced such that each conjugate is aqueously soluble and able to penetrate biological membranes.

93. (New) A pharmaceutical composition comprising:
the mixture according to Claim 72; and
a pharmaceutically acceptable carrier.

94. (New) A method of treating insulin deficiency in a subject in need of such treatment, said method comprising:
administering an effective amount of the mixture of claim 72 to the subject to treat the insulin deficiency.

95. (New) A substantially monodispersed mixture of conjugates each comprising human insulin covalently coupled at Lys^{B29} of the human insulin to the carboxylic acid moiety of a carboxylic acid, which is covalently coupled at the end distal to the carboxylic acid moiety to a methyl terminated polyethylene glycol moiety having at least 7 polyethylene glycol subunits.

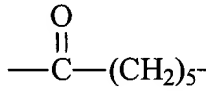
96. (New) The substantially monodispersed mixture according to Claim 95, wherein the carboxylic acid is hexanoic acid.

97. (New) The mixture according to claim 79, wherein at least one of the oligomers comprises a polyethylene glycol moiety having at least 2 polyethylene glycol subunits.

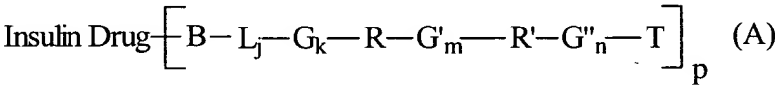
98. (New) The mixture according to claim 79, wherein at least one of the oligomers comprises a polyethylene glycol moiety having at least 5 polyethylene glycol subunits.

99. (New) The mixture according to claim 79, wherein at least one of the oligomers comprises a polyethylene glycol moiety having at least 7 polyethylene glycol subunits.

100. (New) The mixture according to claim 79, wherein the first oligomer has the formula:



101. (New) A substantially monodispersed mixture of conjugates in which each conjugate is the same and has the formula:



(A)

wherein:

B is carbonyl;

L is a linker moiety;

G, G' and G" are individually selected spacer moieties;

R is C_5 alkylene and R' is polyethylene glycol having 7 polyethylene glycol subunits;

T is methoxy;

j is 0 or 1;

k, m and n are 0; and

p is an integer from 1 to the number of nucleophilic residues on the insulin drug.

102. The mixture according to Claim 101, wherein the mixture is monodispersed.